SYNTHESES OF IMIDAZOLES AND PYRROLES: BETMIC AND TOSMIC AS COMPLEMENTARY REAGENTS

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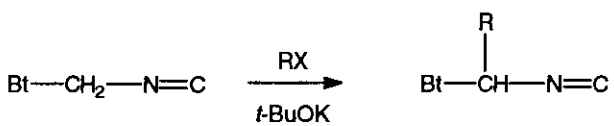
Abstract- *p*-Tolylsulfonylmethyl isocyanide (TosMIC) and benzotriazol-1-yl-methyl isocyanide (BetMIC) were compared as to their synthetic utilities for the synthesis of imidazoles and pyrroles and found to be complementary.

TosMIC (*p*-tolylsulfonylmethyl isocyanide) (1) which embodies the α-anion stabilizing effect of the tosyl and isocyano groups and the electrophilicity of the isocyano group, has become a versatile building block.[1-4] α-Metallated TosMIC possesses a nucleophilic center, which may be added to polar multiple bonds, and an electrophilic center, the isocyanide group, which allows subsequent heterocyclization.[2] This strategy has been applied to the synthesis of oxazoles and oxazolines,[5,6] imidazoles,[6,7] pyrroles,[6,8-11] tosyl substituted thiazoles,[12] ketones[13] and α-hydroxyaldehydes from ketones.[14] The TosMIC methodology has also found application in the modification of steroids,[15,16] synthesis of benzazole rings[17,18] and the preparation of porphyrins.[19] BetMIC (benzotriazol-1-yl-methyl isocyanide) (2) exhibits[20] properties which are qualitatively similar to, but differ quantitatively from those of TosMIC. BetMIC has been used to synthesize α-hydroxyaldehydes (without employing the thallium (I) ethoxide needed with TosMIC) and oxazoles.[20a] Since the benzotriazolyl anion stabilizing group of BetMIC is weaker than tosyl, the BetMIC anion should be more reactive than that of TosMIC which could be advantageous in certain circumstances.

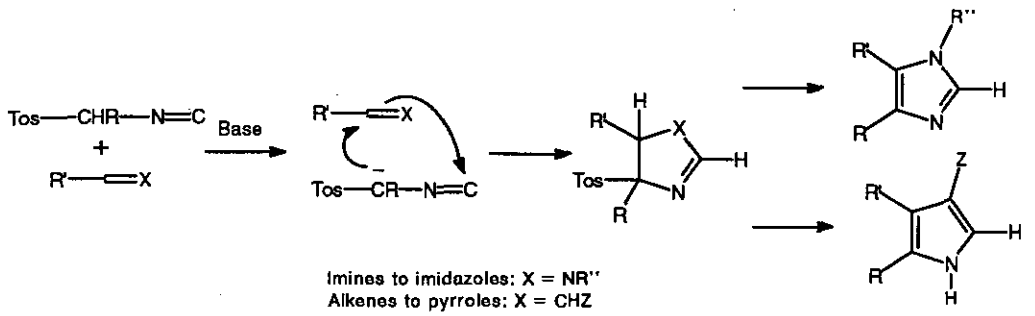
The present paper focuses upon comparison of the utilities of TosMIC and BetMIC in the preparation of imidazoles and pyrroles. The strategy used for this comparative study involved the selection of reactions from the literature for which TosMIC reportedly gave little or no product. The same reactions were attempted with BetMIC to determine if any improvement in the yields of such reactions could be obtained.Some of the present work required that a synthesis of α-alkyl substituted derivatives of BetMIC be developed. The method[21] that gave the best results was employment of potassium *tert*-butoxide as the base in THF.



2

3 R = Me
4 R = CH_2Ph

Preparation of Imidazoles. α-Metallated isocyanides add to imines (Scheme 1; X = NR") to form imidazolines. When a methyl isocyanide with a good leaving group (such as tosyl in TosMIC) is used, imidazoles are often obtained. TosMIC also stabilizes the intermediate carbanion, thus enhancing the reaction. The bases used in these reactions were potassium carbonate, sodium hydride, *t*-butylamine and cyclohexylamine. The yield was found to be determined by the base used and the reaction medium.[2]



Scheme 1. Reaction of α-metallated TosMIC with electrophiles

We now find that BetMIC reacts with aldimines in a similar fashion to TosMIC to form imidazoles. In this case, the benzotriazolyl group stabilizes the anion formed in the first step and is spontaneously eliminated from the intermediate imidazoline. The reactions were attempted in a variety of bases and solvents. BetMIC derivatives were found to be unstable in the presence of strong bases such as LDA, *n*-BuLi and sodium hydride. The most effective conditions for all of these reactions was found to be potassium *tert*-butoxide in DMSO or THF.[22]

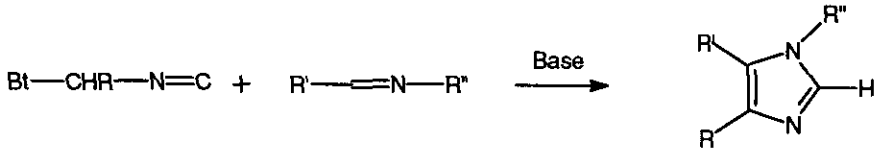


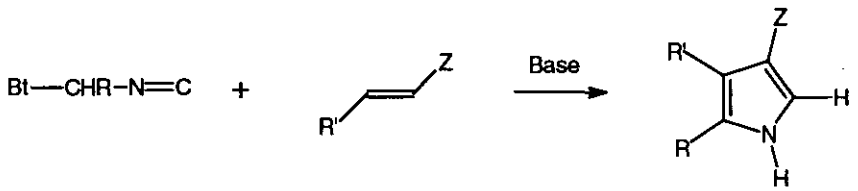
Table 1. Synthesis of Imidazoles: Literature Using TosMIC Compared with the New Route Using BetMIC.

Entry	R	R'	R''	TosMIC	BetMIC		
				Yield (%)	Method[22]	Yield (%)	mp (°C), found (lit.)
1	Me	Ph	p-$NO_2C_6H_4$	75 [6,7]	-	-	-
2	Ph	Ph	Ph	0 [7]	A	23	268-270 (270-272)[23]
3	Me	Ph	Ph	0 [6]	A	67 [a]	97-98
4	$PhCH_2$	p-ClC_6H_4	Ph	68 [6]	-	-	-
5	$PhCH_2$	p-$MeOC_6H_4$	Ph	0 [6]	C	73 [a]	oil
6	H	Ph	Me	10 [7]	A, B, C	10	94-95 (94-95)[7]
7	$PhCH_2$	Ph	Me	0 [6]	A, B	0	-
8	H	Ph	Ph	56 [7]	C	85	130-131 (130-131)[7]

[a]Microanalysis within ±0.4% of the expected values for C, H and N.

Table 1 shows a selection of the reactions reported in the literature using TosMIC: in the case of the reaction of diaryl aldimines, the best results were obtained when an electron withdrawing group is present on at least one of the aryl substituents (Entries 1 and 4).[5,6] Reactions that were reported to give low yields with TosMIC have now been attempted with BetMIC and these results are also shown in Table 1. For diaryl aldimines without electron withdrawing groups, much better yields were obtained with BetMIC than with TosMIC (Entries 2, 3, 5 and 8). In the case of *N*-alkyl aldimines for which TosMIC had produced low yields, BetMIC also gave low yields (Entries 6 and 7).

Preparation of Pyrroles. α-Metallated TosMIC reacts with electron deficient alkenes to form pyrroles (Scheme 1; X = CHZ) in an analogous fashion to its reaction with aldimines to form imidazoles. We now find that BetMIC undergoes a similar reaction with electron deficient alkenes.



Selected literature results of reactions of TosMIC with electron-deficient alkenes[6,8,9] and newly undertaken comparative reactions of BetMIC are shown in Table 2. All the acrylonitriles and the terminally unsubstituted unsaturated esters and ketones gave poor yields of pyrrole when reacted with TosMIC. The use of BetMIC dramatically improved the yields of 3-cyanopyrroles from acrylonitrile derivatives (Entries 8-10) and somewhat improved the yields of 4-unsubstituted 3-methoxycarbonylpyrroles from methyl acrylate (Entries 5 and 7). However for Entries 2 and 3 TosMIC gave better results than BetMIC.

Table 2. Synthesis of Pyrroles: Literature Using TosMIC Compared with the New Route Using BetMIC.

Entry	R	R'	Z	TosMIC	BetMIC		
				Yield (%)	Method[24]	Yield (%)	mp (°C), found (lit)
1	H	Ph	COMe	70 [8]	-	-	-
2	H	H	COMe	15 [8]	A	0	(110-111) [8]
3	H	Ph	COOMe	70 [8]	A	40	181-183 (182-183) [8]
4	H	Me	COOMe	64 [8]	-	-	-
5	H	H	COOMe	33 [8]	A	45	86-88 (86-87) [8]
6	Ph	Ph	COOMe	45 [25]	-	-	-
7	Me	H	COOMe	0 [6]	B	30	114-115 (117-118) [25]
8	H	Ph	CN	35 [8]	A	81	126-127 (128-129) [8]
9	H	Me	CN	50 [8]	A	92	114 (114-117) [8]
10	H	H	CN	10 [8]	A	63	54-55 (53-55) [8]

Conclusion. BetMIC represents a useful alternative to TosMIC for the synthesis of imidazoles and pyrroles with less reactive electrophiles.

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21. Potassium *tert*-butoxide (6 mmol) in THF (10 ml) was added dropwise to a stirred mixture of BetMIC (0.79g, 5 mmol) and methyl iodide (0.71g) or benzyl chloride (0.63g) (5 mmol), in THF (20 ml) at -78 °C. The reaction mixture was allowed to warm to room temperature, water was added, the solution extracted with ether, the ether extract dried ($MgSO_4$) and evaporated to dryness. Column chromatography (silica, ethyl acetate/hexane 1:3) gave, as oils, isolated yields of 53% for 1-(benzotriazol-1-yl)ethyl isocyanide (**3**) and 50% for 1-(benzotriazol-1-yl)-2-phenylethyl isocyanide (**4**). Microanalytical data was within ±0.4% of the expected values for C and H.

22. **Method A:** To a stirred solution of BetMIC (or derivative) (5 mmol) and aldimine (5 mmol) in THF (25 ml) at 0 °C was added a solution of potassium *tert*-butoxide (1.12g, 10 mmol) in THF (15 ml). The reaction mixture was heated to reflux, cooled, evaporated to dryness and the residue extracted with ether. The extracts were evaporated to dryness and the residue subjected to column chromatography (silica, ethyl acetate/hexane 1:1). **Method B:** This procedure is similar to the above method except that a solution of BetMIC (or derivative) (5 mmol) in THF (15 ml) was added dropwise to a mixture of the aldimine (5 mmol) and potassium *tert*-butoxide (1.12g, 10 mmol) in THF (15 ml). The reaction mixture was heated to reflux and the procedure continued as above. **Method C:** This procedure is similar to the above Method A except that DMSO (rather than THF) was used as the solvent, addition took place at room temperature and that after heating to 75 °C, the mixture was cooled, diluted with water and extracted with ether. The ether extracts were washed with water and dried ($MgSO_4$), evaporated to dryness and the residue subjected to column chromatography (silica, ethyl acetate/hexane 1:1).

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24. **Method A:** To a stirred solution of BetMIC (or derivative) (5 mmol) and alkene (5 mmol) in THF (25 ml) at 0 °C was added a solution of potassium *tert*-butoxide (1.12g, 10 mmol) in THF (15 ml). The reaction mixture was heated to reflux, cooled, water was added, the solution brought to a pH of 5 with 10% HCl and the mixture extracted with ether. The dried extracts ($MgSO_4$) were evaporated to dryness and the residue subjected to column chromatography (silica, ethyl acetate/hexane 1:1). **Method B:** This procedure is similar to the above method except that a solution of potassium *tert*-butoxide (1.12g, 10 mmol) in THF (15 ml) was added to a solution of BetMIC (or derivative) in THF (15 ml) at -78 °C. The electrophile was then added dropwise, the mixture was warmed slowly to room temperature, heated to reflux and the procedure continued as above.

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